## REMARKS

Claims 1-52 were pending in the instant application. Upon entry of the present Amendment, claims 1-52 are pending and presented for reconsideration. Applicants respectfully submit that no new matter is introduced by the present Amendment.

Amendment and/or cancellation of the claims is not to be construed as acquiescence to any of the objections/rejections set forth in the instant Office Action or any previous Office Action of the parent application, and was done solely to expedite prosecution of the application. Applicants submit that claims were not added or amended during the prosecution of the instant application for reasons related to patentability. Applicants reserve the right to pursue the claims, as originally filed, or similar claims in this or one or more subsequent patent applications.

### *Rejection of Claims 1-6 and 52 Under 35 U.S.C. § 112, First Paragraph*

The Examiner has rejected claims 1-6 and 52 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner is of the opinion that "the specification does not teach adequate support for the claimed 'downmodulates' or 'downmodulation'."

Applicants traverse the foregoing rejection on the grounds that the instant specification sufficiently describes the claimed invention so that a skilled artisan would recognize that Applicants were in possession of the claimed invention at the time of filing. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

Applicants respectfully submit that it is an established principle of U.S. patent law that the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement as long as the newly added claim limitations are supported in the specification through express, implicit, or inherent disclosure. See M.P.E.P.§ 2163 and § 2163.02. In the present case, the claim limitations "downmodulate" and "downmodulation" are supported in the specification through express, implicit, and inherent disclosure.

Contrary to the Examiner's assertions, written support can be found in the originally filed specification for the limitations "downmodulate" and "downmodulation." Specifically, Applicants teach in the specification at least at page 18, line 32 through page 19, line 32, that

> [t]he term "transcription factor modulating compound" or "transcription factor modulator" includes compounds which ***modulate transcription***, *i.e.*, which ***affect the expression and/or activity*** of one or more transcription factors, such that the expression and/or activity of the transcription factor is modulated, *e.g.*, enhanced or ***inhibited***...
> The term "HTH protein modulating compound" or "HTH protein modulator" includes compounds which interact with one or more proteins comprising an HTH domain such that the activity of the HTH protein is modulated, *e.g.*, enhanced or, ***inhibited***. In one embodiment, the HTH protein modulating compound is a MarA family polypeptide modulating compound... In a preferred embodiment, ***the activity of the HTH protein is decreased upon an interaction with the HTH protein modulating compound***... (Emphasis added).

The compounds of the invention ***downmodulate*** the expression or activity of a microbial transcription factor. At page 19, Applicants make the distinction between modulating expression or activity by ***downmodulating*** expression or activity, *e.g.*, inhibiting expression or activity (encompassed by the invention) and ***up-regulating*** expression or activity, *e.g.*, enhancing expression or activity. Moreover, Applicants provide numerous examples of compounds which downmodulate expression or activity of a microbial transcription factor at least in Examples 2 and 3 at pages 120-122 of the specification. Applicants also demonstrate that these compounds ***downmodulate*** microbial transcription factor expression or activity both *in vitro* and in the *in vivo* urinary tract infection molecule (see, *e.g.*, Example 7 at pages 126-127 of the specification, as filed).

Based on the foregoing teachings in the specification, one of ordinary skill in the art would conclude that there is implicit and inherent disclosure in the specification regarding compounds which downmodulate the expression or activity of a microbial transcription factor and would conclude that Applicants were in possession of the claimed genus of compounds. As indicated above, the subject matter of the claim need not be described literally in order for the disclosure to satisfy the description requirement as long as the newly added claim limitations are supported in the specification through express, implicit, or inherent disclosure. See M.P.E.P.§

2163 and § 2163.02. Accordingly, Applicants respectfully request that the aforementioned rejection of claims 1-11 under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

***Rejection of Claims 1-6 and 52 under 35 U.S.C. §112, First Paragraph***

Claims 1-6 and 52 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Office Action states that "[t]he specification as currently presented while describing the treatment of a microbial infection via administering a modulator of a transcription factor to an individual in need thereof does not provide support for a method to prevent said infecting in an individual." Applicants traverse the foregoing rejection on the grounds that one of ordinary skill in the art would understand that Applicants were in possession of the claimed invention.

The pending claims are directed to a method for an preventing infection, *e.g.,* prostatitis or urinary tract infection, of a subject by a microbe comprising: administering a compound that downmodulates the expression or activity of a microbial transcription factor to a subject at risk of developing an infection, wherein the downmodulation of the microbial transcription factor reduces the virulence of the microbe, such that infection is prevented. For the reasons set forth below, Applicants respectfully submit that the claimed invention is supported by the specification on record and that the instant specification conveys to the ordinary skilled artisan that the inventors had possession of the claimed invention at the time the application was filed.

An objective standard for determining compliance with the written description requirement under 35 U.S.C. § 112, first paragraph, is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, the applicant was in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) and *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

To begin with, the Examiner has admitted, at page 5 of the Final Office Action mailed from the U.S. Patent and Trademark Office on September 8, 2006, that the specification adequately describes "the ***treatment of a microbial infection*** via administering a modulator of a transcription factor to an individual in need thereof." (Emphasis added). Applicants respectfully submit that Applicants' specification also provides extensive teachings on methods for ***preventing infection*** of a subject by a microbe by administering a compound that

downmodulates the expression or activity of a microbial transcription factor to a subject at risk of developing an infection, wherein the downmodulation of the microbial transcription factor reduces the virulence of the microbe, such that infection is prevented.

Applicants respectfully submit that the inhibitory compounds of the invention have no intrinsic antibacterial activity (see, *e.g.*, page 37, third full paragraph). These claimed compounds do not affect the bacteria's ability to grow and have no direct effect on the bacteria other than ***preventing the initial infectious process***.

Applicants respectfully submit that the specification provides a plethora of teachings on how to generate and test the claimed compounds for functional activity. For example, the specification teaches at least at page 38, line 1 through page 50, line 3, a multitude of whole cell assays that can be performed in order to determine whether a compound downmodulates the activity or expression of a transcription factor by contacting a cell expressing a transcription factor with a compound and measuring the ability of the compound to modulate the activity and/or expression of a transcription factor. Specifically, Applicants teach at least at page 38, lines 26-29, that "transcription of a transcription factor gene can be measured in control cells which have not been treated with the compound and compared with that of test cells which have been treated with the compound…" and that transcription can be determined by measuring the amount of RNA produced by the cell (see, *e.g.*, page 39, lines 19-31), by measuring the amount of transcription factor produced by a cell (see, *e.g.*, page 39, line 32 through page 40, line 6), by detecting other sequences which are regulated by a transcription factor, *e.g.*, using a reporter gene (see, *e.g.*, page 40, line 7 through page 41, line 30), by measuring the binding of a transcription factor to a transcription factor binding molecule (see, *e.g.*, page 41, lines 31 through page 42, line 2), etc. Additionally, Applicants' specification teaches at least at page 50, line 8 through page 58, line 2, cell-free assays for screening for inhibitors of transcription factors. Furthermore, Figure 3 exemplifies cell-free assays of Mar inhibitors.

Not only do Applicants teach methods for the generation and testing of the claimed compounds for activity *in vitro*, but Applicants also teach *in vivo* models of suitable for testing the ability of the claimed compounds to prevent infection of a subject. Applicants' specification explicitly teaches at least at pages 126-127, Example 7, two inhibitors of transcription factors that were tested in a working example, the urinary tract infection model. In this experiment, Applicants teach that "mice were treated once, at the time of infection," and treatment with a dose of 100 mg/kg of inhibitor ***prevented infection in 100% of the mice tested***, *e.g.*, 0 out of 5

mice were infected (see, *e.g.*, the chart on page 127 of the specification). Furthermore, Applicants further teach that lower doses of inhibitor, *e.g.*, 10 mg/kg and 1 mg/kg, can also prevent infection in a substantial percentage of the mice (see, *e.g.*, the chart on page 127 of the specification).

The specification also provides extensive teachings on how to prevent infection using inhibitors of transcription factors in animal models, *e.g.*, in the pyelonephritis model of infection. At, for example, page 132, lines 28-31 of the specification, Applicants teach that "***the administration of a single subcutaneous dose of the inhibitor at the time of infection was sufficient to prevent infection in this [pyelonephritis] in vivo model***." Figure 10 exemplifies these results, and similar results were also observed using smaller doses with multiple dose regiments (see, *e.g.*, Figure 10 and page 132, lines 31-33 of the specification).

In addition to the foregoing extensive teachings in Applicants' specification, Applicants provide teachings regarding the composition for administration for a method of prophylaxis. For example, Applicants teach pharmaceutical compositions at least at page 84, line 9, through page 90, line 34. Specifically, Applicants teach several routes of administration and typical ingredients of the composition, based upon the route of administration. The specification also discloses exemplary doses, including milligram or microgram amounts of the small molecule per kilogram of subject, *e.g.*, about 1 microgram per kilogram to about 500 micrograms per kilogram, about 100 micrograms per kilogram to about 5 micrograms per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram (see *e.g.*, page 90, lines 17-21 of the specification). Further, Applicants state that "it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression and/or activity to be modulated" (see, *e.g.*, page 90, lines 29-34).

The Examiner has alleged that "in all of the examples given, a compound has not been identified that convincingly demonstrates prevention of infection, only statement 'compound can be identified' has been made even where an experiment has been described." In contrast to the Examiner's assertions, Applicants provide numerous ***in vivo working examples*** which exemplify the claimed methods and compounds (see, *e.g.*, Example 7 and Example 12). In these *in vivo* infection models, Applicants introduce the bacteria into the ***bladder*** of the mouse (see, *e.g.*, page

124, Example 6 of the specification) and concurrently treat the mice with a dose of inhibitor compound. After a designated period of time, the mice are sacrificed, and their ***kidneys*** are removed. In other words, Applicants are inoculating the bladder with bacteria and looking for ***migration of the bacteria to the kidneys, where any resulting kidney infection may occur***. Accordingly, by concurrently dosing the mice with inhibitor compound at the time of bacterial exposure to the ***bladder***, Applicants are demonstrating that ***infection of the kidneys is prevented***. Specifically, in Example 7 Applicants provide teachings regarding the composition for administration for a method of prophylaxis in such a urinary tract infection animal model. In one such experiment, Applicants teach that "mice were treated once, at the time of infection," with the claimed compounds and treatment with a dose of 100 mg/kg of inhibitor compound ***prevented infection in 100% of the mice tested***, *e.g.*, 0 out of 5 mice were infected (see, *e.g.*, the chart on page 127 of the specification). Furthermore, Applicants further teach that lower doses of inhibitor compound, *e.g.*, 10 mg/kg and 1 mg/kg, can also prevent infection in a substantial percentage of the mice (see, *e.g.*, the chart on page 127 of the specification). In a subsequent experiment (see Example 12 on page 132 of the specification), the efficacy of one prototypic inhibitor was investigated in the ascending pyelonephritis model of infection. The administration of a single subcutaneous dose of the inhibitor at the time of infection was sufficient to prevent infection in this *in vivo* model (see Figure 10 of the specification). Furthermore, the specification teaches at page 132, lines 29-33, that "[r]esults similar to those obtained with the single 100 mg/kg dose (Fig. 10) were observed using smaller doses with multiple dose regimens (bid x4 d, data not shown)."

Additional evidence, attached herein as Appendix A, also demonstrates that microbial infection is prevented using the claimed methods. For example, as indicated by Figure 1 of the attached Appendix A, inhibitory compounds (P005260, P005203 and P005330) of the MarA-family member, LcrF, prevent *Y. pseudotuberculosis* infection in a lethal murine pneumonia model. Specifically, mice were dosed with an inhibitory compound at 1 day prior to inocluation, at the time of inocluation, at 8 hours post-inocluation, and then daily for 8 days following intranasal bacterial inoculation. As indicated in Figure 1, ***administration of an inhibitory compound, either P005260, P005203 or P005330, prevented of infection and led to survival of up to 50% to 75% of the mice*** as compared to the control where mice were not dosed with an inhibitory compound and infection was prevented in 0% of the mice.

Similarly, Figures 2A and 2B of the attached Appendix A demonstrate that the inhibitory compounds P005631 and P005301 of the MarA family member ExsA prevent *Pseudomonas aeruginosa* infection in a mouse lethal pneumonia model. Mice were dosed at 18 hours prior to inoculation, at 1 hour prior to inoculation, and at 2, 5, 20, 26 and 44 hours following intranasal bacterial inoculation. Figures 2A and 2B demonstrate that ***administration of the inhibitory compounds prevented infection and led to survival of approximately 45% to 55% of the inoculated mice*** as compared to the control where mice were not dosed with an inhibitory compound and only 10% to 20% of the mice survived.

Figure 3 of the attached Appendix A further demonstrates that inhibitory compounds (P005260, P005203 and P005330) of the MarA-family member LcrF prevent *Y. pseudotuberculosis* infection in a non-lethal lung infection model. In this non-lethal lung infection model, mice were dosed with an inhibitory compound at 1 day prior to inocluation, at the time of inocluation, at 8 hours post-inocluation, and then once daily for 2 days following intranasal bacterial inoculation. These data demonstrate that ***administration of an inhibitory compound, either P005260, P005203 or P005330, leads to a 0.8 to 1.5 log decrease in CFU (colony forming units) per gram of lung tissue*** as compared to control mice that were inoculated with wild-type *Y. pseudotuberculosis* and not dosed with an inhibitory compound. In other words, administration of the inhibitory compounds led to a substantial prevention of *Y. pseudotuberculosis* infection in the non-lethal lung infection model.

Finally, the MarA targets, themselves, have been validated in the art. For example, if a MarA family member gene is knocked-out in a bacterial strain, the bacterial strain is rendered avirulent and any subsequent bacterial infection is ***prevented***. Figure 4 of the attached Appendix A demonstrates that knocking out the ExsA gene, a MarA family member, leads to 100% survival of mice in a lethal *Pseudomonas aeruginosa* murine pneumonia model. Thus, ***knocking out MarA transcription factor genes or inhibiting MarA transcription factor activity renders bacteria avirulent and prevents the establishment of infection***[1].

In conclusion, based on the foregoing teachings and references incorporated into Applicants' specification, as well as the general knowledge in the art at the time of the invention,

[1] See also Casaz *et al.,* Microbiology, 152:3642-50 (2006) and Munson *et al.,* Infection and Immunity, 69:186-93 (2001), attached herein as Appendix B.

one of skill in the art would recognize that Applicants were in possession of the claimed invention. Applicants, therefore, respectfully request withdrawal of the rejection of claims 1-6 and 52 under 35 U.S.C. §112, first paragraph and favorable reconsideration.

## CONCLUSION

In view of the above amendments and remarks, Applicants believe that the pending application is in condition for allowance. Applicants believe that no additional fee is due with this communication. However, if an additional fee is due, please charge our Deposit Account No. 12-0080, under Order No. PAZ-190RCE from which the undersigned is authorized to draw.

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Respectfully submitted,

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